Neuropathic pain

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Abstract | Neuropathic pain is caused by a lesion or disease of the somatosensory system, including peripheral fibres (Aβ, Aδ and C fibres) and central neurons, and affects 7–10% of the general population. Multiple causes of neuropathic pain have been described and its incidence is likely to increase owing to the ageing global population, increased incidence of diabetes mellitus and improved survival from cancer after chemotherapy. Indeed, imbalances between excitatory and inhibitory somatosensory signalling, alterations in ion channels and variability in the way that pain messages are modulated in the central nervous system all have been implicated in neuropathic pain. The burden of chronic neuropathic pain seems to be related to the complexity of neuropathic symptoms, poor outcomes and difficult treatment decisions. Importantly, quality of life is impaired in patients with neuropathic pain owing to increased drug prescriptions and visits to health care providers, as well as the morbidity from the pain itself and the inciting disease. Despite challenges, progress in the understanding of the pathophysiology of neuropathic pain is spurring the development of new diagnostic procedures and personalized interventions, which emphasize the need for a multidisciplinary approach to the management of neuropathic pain.

Although distinct definitions of neuropathic pain have been used over the years, its most recent (2011) and widely accepted definition is pain caused by a lesion or disease of the somatosensory system. The somatosensory system allows for the perception of touch, pressure, pain, temperature, position, movement and vibration. The somatosensory nerves arise in the skin, muscles, joints and fascia and include thermoreceptors, mechanoreceptors, chemoreceptors, pruriceptors and nociceptors that send signals to the spinal cord and eventually to the brain for further processing (BOX 1); most sensory processes involve a thalamic nucleus receiving a sensory signal that is then directed to the cerebral cortex. Lesions or diseases of the somatosensory nervous system can lead to altered and disordered transmission of sensory signals into the spinal cord and the brain; common conditions associated with neuropathic pain include postherpetic neuralgia, trigeminal neuralgia, painful radiculopathy, diabetic neuropathy, HIV infection, leprosy, amputation, peripheral nerve injury pain and stroke (in the form of central post-stroke pain) (FIG. 1). Not all patients with peripheral neuropathy or central nervous injury develop neuropathic pain; for example, a large cohort study of patients with diabetes mellitus indicated that the overall prevalence of neuropathic pain symptoms was 21% in patients with clinical neuropathy. However, the prevalence of neuropathic pain increased to 60% in those with severe clinical neuropathy[1]. Importantly, neuropathic pain is mechanistically dissimilar to other chronic pain conditions such as inflammatory pain that occurs, for example, in rheumatoid arthritis, in which the primary cause is inflammation with altered chemical events at the site of inflammation; such pain is diagnosed and treated differently[2].

Neuropathic pain is associated with increased drug prescriptions and visits to health care providers[3,4]. Patients typically experience a distinct set of symptoms, such as burning and electrical-like sensations, and pain resulting from non-painful stimulations (such as light touching); the symptoms persist and have a tendency to become chronic and respond less to pain medications. Sleep disturbances, anxiety and depression are frequent and severe in patients with neuropathic pain, and quality of life is more impaired in patients with chronic neuropathic pain than in those with chronic non-neuropathic pain that does not come from damaged or irritated nerves[3,5].

Despite the increases of placebo responses[6,7] that result in the failure of multiple new drugs in clinical trials, recent progress in our understanding of the pathophysiology of neuropathic pain provides optimism for the development of new diagnostic procedures and

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personalized interventions. This Primer presents the current descriptions of the presentation, causes, diagnosis and treatment of neuropathic pain, with a focus on peripheral neuropathic pain given that our knowledge is greater than that of central neuropathic pain.

Epidemiology

The estimation of the incidence and prevalence of neuropathic pain has been difficult because of the lack of simple diagnostic criteria for large epidemiological surveys in the general population. Thus, the prevalence of neuropathic pain in the chronic pain population has mainly been estimated on the basis of studies[8] conducted by specialized centres with a focus on specific conditions, such as postherpetic neuralgia[9,10], painful diabetic polyneuropathy[1,11–13], postsurgery neuropathic pain[14], multiple sclerosis[15,16], spinal cord injury[17], stroke[18] and cancer[19,20].

The recent development of simple screening tools in the form of questionnaires[21] has helped conduct several large epidemiological surveys in different countries (the United Kingdom, the United States, France and Brazil) and provided valuable new information on the general prevalence of neuropathic pain[4]. In using screening tools, such as the Douleur Neuropathique 4 questions (DN4)[22] or the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale[23] (BOX 2), the prevalence of chronic pain with neuropathic characteristics has been estimated to be in the range of 7–10%[8,24].

Chronic neuropathic pain is more frequent in women (8% versus 5.7% in men) and in patients >50 years of age (8.9% versus 5.6% in those <49 years of age), and most commonly affects the lower back and lower limbs, neck and upper limbs[24]. Lumbar and cervical painful radiculopathies are probably the most frequent cause of chronic neuropathic pain. Consistent with these data, a survey of >12,000 patients with chronic pain with both nociceptive and neuropathic pain types, referred to pain specialists in Germany, revealed that 40% of all patients experience at least some characteristics of neuropathic pain (such as burning sensations, numbness and tingling); patients with chronic back pain and radiculopathy were particularly affected[25].

Mechanisms/pathophysiology

Research in the pain field has focused on understanding the plastic changes in the nervous system after nerve injury, identifying novel therapeutic targets and in facilitating the transfer of knowledge from animal models to clinical practice. We describe briefly the multiple causes of neuropathic pain and present an overview of animal and human findings that have provided insights on the pathophysiology of neuropathic pain.

Causes and distributions

Central neuropathic pain is due to a lesion or disease of the spinal cord and/or brain. Cerebrovascular disease affecting the central somatosensory pathways (post-stroke pain) and neurodegenerative diseases (notably Parkinson disease) are brain disorders that often cause central neuropathic pain[26]. Spinal cord lesions or diseases that cause neuropathic pain include spinal cord injury, syringomyelia and demyelinating diseases, such as multiple sclerosis, transverse myelitis and neuromyelitis optica[27]. By contrast, the pathology of the peripheral disorders that cause neuropathic pain predominantly involves the small unmyelinated C fibres and the myelinated A fibres, namely, the Aβ and Aδ fibres[5]. Peripheral neuropathic pain will probably become more common because of the ageing global population, increased incidence of diabetes mellitus and the increasing rates of cancer and the consequence of chemotherapy, which affect all sensory fibres (Aβ, Aδ and C fibres). Peripheral neuropathic pain disorders can be subdivided into those that have a generalized (usually symmetrical) distribution and those that have a focal distribution (FIG. 2). The most clinically important painful generalized peripheral neuropathies include those associated with diabetes mellitus (BOX 3), pre-diabetes and other metabolic dysfunctions, infectious diseases (mainly HIV infection[28] and leprosy[29]), chemotherapy, immune (for example, Guillain–Barré syndrome) and inflammatory disorders, inherited neuropathies and channelopathies (such as inherited erythromelalgia, a disorder in which blood vessels are episodically blocked then become hyperaemic and inflamed).

The topography of the pain in these disorders typically encompasses the distal extremities, often called a 'glove and stocking' distribution because the feet, calves, hands and forearms are most prominently affected. This distribution pattern is characteristic of dying-back, length-dependent, distal peripheral neuropathies involving a distal–proximal progressive sensory loss, pain and, less frequently, distal weakness. Less frequently, the pain has a proximal distribution in which the trunk, thighs and upper arms are particularly affected; this pattern occurs when the pathology involves

the sensory ganglia. Painful focal peripheral disorders are caused by pathological processes that involve one or more peripheral nerves or nerve roots. These disorders include postherpetic neuralgia, post-traumatic neuropathy, postsurgical neuropathy, cervical and lumbar polyradiculopathies, pain associated with HIV infection, leprosy and diabetes mellitus, complex regional pain syndrome type 2 and trigeminal neuralgia[30].

Rare inherited channelopathies can show characteristic pain distributions and triggering factors. For example, inherited erythromelalgia is due to mutations in *SCN9A*, which encodes the voltage-gated sodium channel $Na_v1.7$ (involved in the generation and conduction of action potentials), and is characterized by pain and erythema (reddening) in the extremities, which is exacerbated by heat[31]. Paroxysmal extreme pain disorder is due to a distinct set of mutations in *SCN9A* that result in a proximal distribution of pain and erythema affecting the sacrum and mandible[32]; pain triggers in those with this condition can include mechanical stimuli. In approximately 30% of patients with idiopathic small-fibre neuropathy, functional mutations of the $Na_v1.7$ sodium channel that result in hyperexcitable dorsal root ganglion neurons have been observed[33].

Pain signalling changes

Peripheral neuropathy alters the electrical properties of sensory nerves, which then leads to imbalances between central excitatory and inhibitory signalling such that inhibitory interneurons and descending control systems are impaired. In turn, transmission of sensory signals and disinhibition or facilitation mechanisms are altered at the level of the spinal cord dorsal horn neurons. Indeed, preclinical studies have revealed several anatomical, molecular and electrophysiological changes from the periphery through to the central nervous system (CNS) that produce a gain of function, providing insights into neuropathic pain and its treatment (BOX 4). At the periphery, spinal cord and brain, a gain of excitation and facilitation and a loss of inhibition are apparent. These changes shift the sensory pathways to a state of hyperexcitability, and a sequence of changes over time from the periphery to the brain might contribute to the neuropathic pain state becoming chronic.

Ectopic activity in primary afferent fibres might have a key role in the pathophysiology of neuropathic pain following peripheral nerve injury. Patients with painful diabetic polyneuropathy and traumatic peripheral nerve injury showed a complete loss of ipsilateral spontaneous

Box 1 | **Key terms**

Action potential
An electrical event in which the membrane potential of a cell in the nervous system rapidly rises and falls to transmit electrical signals from cell to cell.

Allodynia
Pain caused by a normally non-painful stimulus.

Aβ fibres
Sensory nerve fibres with a thick myelin sheath, which insulates the axon of the cell and normally promotes the conduction of touch, pressure, proprioception and vibration signals (35–90 metres per second).

Aδ fibres
Sensory nerve fibres with a myelin sheath, which insulates the axon of the cell and promotes the conduction of cold, pressure and pain signals (5–30 metres per second), that produce the acute and sharp experience of pain.

C fibres
Unmyelinated pain nerve fibres that respond to warmth and a range of painful stimuli by producing a long-lasting burning sensation due to a slow conduction speed (0.5–2 metres per second).

Chemoreceptors
Receptors that transduce chemical signals.

Complex regional pain syndromes
Also known as causalgia and reflex sympathetic dystrophy, complex regional pain syndromes are conditions that are characterized by the presence of chronic, intense pain (often in one arm, leg, hand or foot) that worsens over time and spreads in the affected area. These conditions are typically accompanied by a colour or temperature change of the skin where the pain is felt.

Conditioned pain modulation
A reduction of a painful test stimulus under the influence of a conditioning stimulus.

Dynamic mechanical allodynia
A type of mechanical allodynia that occurs when pain is elicited by lightly stroking the skin.

Expectancy-induced analgesia
A reduction of pain experience due to anticipation, desire and belief of hypoalgesia or analgesia.

Hyperalgesia
A heightened experience of pain caused by a noxious stimulus.

Hypoalgesia
A decreased perception of pain caused by a noxious stimulus.

Mechanoreceptors
A sensory receptor that transduces mechanical stimulations.

Nociceptors
A peripheral nervous system receptor that is responsible for transducing and encoding painful stimuli.

Paradoxical heat sensation
An experienced sensation of heat provoked by a cold stimulus.

Provoked pain
Pain provoked by applying a stimulus.

Pruriceptors
Sensory receptors that transduce itchy sensations.

Second-order nociceptive neurons
Nociceptive neurons in the central nervous system that are activated by the Aβ, Aδ and C afferent fibres and convey sensory information from the spinal cord to other spinal circuits and the brain.

Static pain
Another kind of mechanical hyperalgesia in those with neuropathic pain when pain is provoked after gentle pressure is applied on the symptomatic area.

Temporal summation
The phenomenon in which progressive increases in pain intensity are experienced during the repetition of identical nociceptive stimuli.

Thermoreceptors
Sensory receptors that respond to changes in temperature.

and evoked pain when treated with a peripheral nerve block (with lidocaine, which blocks voltage-gated sodium channels)[34]. Similarly, a blockade of the dorsal root ganglion by intraforaminal epidural administration of lidocaine resulted in relief of painful and non-painful sensations in patients with phantom limb pain[35]. Microneurography studies have also identified a spontaneous activity — primarily in C fibres — that is related to pain, suggesting a potential peripheral mechanism for neuropathic pain[36,37].

Overall, the underlying hyperexcitability in neuropathic pain results from changes in ion channel function and expression, changes in second-order nociceptive neuronal function and changes in inhibitory interneuronal function.

Ion channel alterations. Neuropathy causes alterations in ion channels (sodium, calcium and potassium) within the affected nerves, which can include all types of afferent fibres that then affect spinal and brain sensory signalling. For example, increased expression and function of sodium channels at the spinal cord terminus of the sensory nerves (mirrored by an enhanced expression of the $\alpha_2\delta$ subunit of calcium channels)

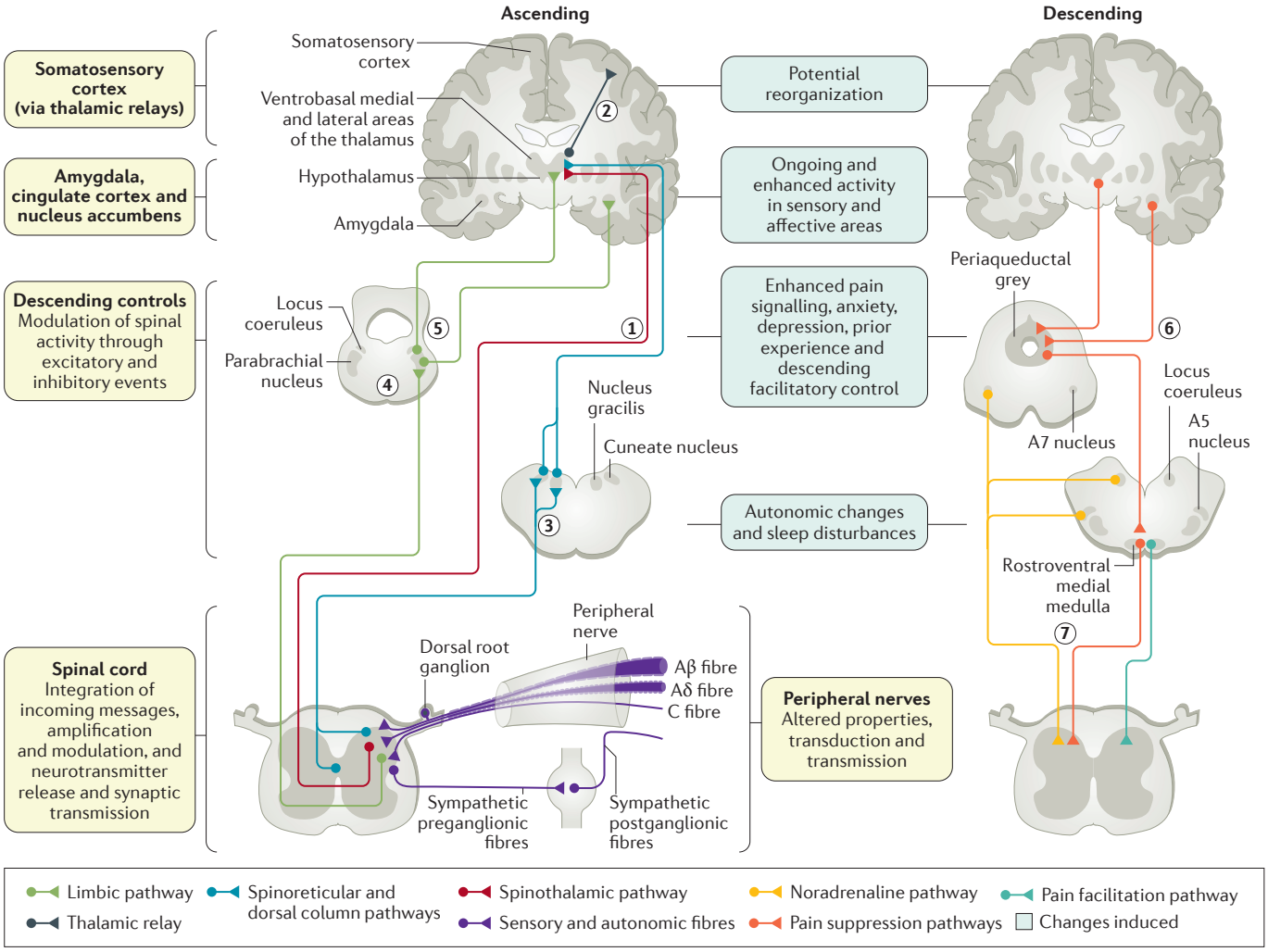

Figure 1 | **The peripheral and central changes induced by nerve injury or peripheral neuropathy.** Preclinical animal studies have shown that damage to all sensory peripheral fibres (namely, Aβ, Aδ and C fibres; BOX 1) alters transduction and transmission due to altered ion channel function. These alterations affect spinal cord activity, leading to an excess of excitation coupled with a loss of inhibition. In the ascending afferent pathways, the sensory components of pain are via the spinothalamic pathway to the ventrobasal medial and lateral areas (1), which then project to the somatosensory cortex allowing for the location and intensity of pain to be perceived (2). The spinal cord also has spinoreticular projections and the dorsal column pathway to the cuneate nucleus and nucleus gracilis (3). Other limbic projections relay in the parabrachial nucleus (4) before contacting the hypothalamus and amygdala, where central autonomic function, fear and anxiety are altered (5). Descending efferent pathways from the amygdala and hypothalamus (6) drive the periaqueductal grey, the locus coeruleus, A5 and A7 nuclei and the rostroventral medial medulla. These brainstem areas then project to the spinal cord through descending noradrenaline (inhibition via α_2 adrenoceptors), and, in neuropathy, there is a loss of this control and increased serotonin descending excitation via 5-HT_3 receptors (7). The changes induced by peripheral neuropathy on peripheral and central functions are shown. Adapted with permission from REF. 38, Mechanisms and management of diabetic painful distal symmetrical polyneuropathy, American Diabetes Association, 2013. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

Box 2 | **Validated screening tools for neuropathic pain**

Symptom and clinical examination items can be assessed using distinct validated screening tools. The most common tools are listed below.

Leeds Assessment of Neuropathic Symptoms and Signs*

- Four symptom items (pricking, tingling, pins and needles; electric shocks; hot or burning sensations; and pain evoked by light touching)
- One item related to skin appearance (mottled or red)
- Two clinical examination items (touch-evoked allodynia and altered pinprick sensation)

Douleur Neuropathique 4 questions‡

- Seven symptom items (burning, painful cold, electric shocks, tingling, pins and needles, numbness and itching)
- Three clinical examination items (touch hypoaesthesia (reduced sense), pinprick hypoaesthesia and brush-evoked allodynia)

Neuropathic Pain Questionnaire§

- Seven sensory descriptors (burning pain, shooting pain, numbness, electrical-like sensations, tingling pain, squeezing pain and freezing pain)
- Three items related to provoking factors (overly sensitive to touch, touch-evoked pain and increased pain due to weather change)
- Two items describing affect (unpleasantness and overwhelming)

painDETECT‖

- Seven weighted symptom items (burning, tingling or prickling, touch-evoked pain, electric shocks, temperature-evoked pain, numbness and pressure-evoked pain)
- Two items related to spatial (radiating pain) and temporal characteristics

ID Pain¶

- Five symptom items (pins and needles, hot or burning, numbness, electrical shocks and touch-evoked pain)
- One item related to location (joints)

Neuropathic Pain Symptom Inventory#

- Ten descriptors (burning, pressure, squeezing, electrical shocks, stubbing, pain evoked by brushing, pain evoked by pressure, pain evoked by cold stimuli, pins and needles, and tingling)
- Two temporal items (the temporal sequence of spontaneous ongoing pain and paroxysmal pain)
- Five clinically relevant dimensions (evoked pain, paroxysmal pain, abnormal sensations, superficial and deep components of spontaneous ongoing pain)

*See REF. 23. ‡See REF. 22. §See REF. 195. ‖See REF. 64. ¶See REF. 196. #See REF. 65.

lead to increased excitability, signal transduction and neurotransmitter release. Indeed, the crucial role of sodium channels is shown by loss or gain of pain in humans with inherited channelopathies[31]. At the same time, a loss of potassium channels that normally modulate neural activity is also evident. If an afferent fibre is disconnected from the periphery due to an injury or a lesion, there will be sensory loss. However, the remnants of the fibres at the injury site can generate ectopic activity (for example, neuroma C fibre afferents), and so pain from a 'numb' area results[38]. The remaining intact fibres are hyperexcitable, so-called irritable nociceptors[39]. As a result, the patient can experience ongoing pain, numbness and evoked pains. The altered inputs into the spinal cord coupled with increased calcium channel function (through higher expression in the nerve terminal) result in increased neurotransmitter release and enhanced excitatory synaptic transmission in the nociceptive circuit.

Second-order nociceptive neuron alterations. Enhanced excitability of spinal neurons produces increased responses to many sensory modalities, enables low-threshold mechanosensitive Aβ and Aδ afferent fibres to activate second-order nociceptive neurons (which convey sensory information to the brain) and expands their receptive fields so a given stimulus excites more second-order nociceptive neurons, generating the so-called central sensitization[40,41]. In particular, ongoing discharge of peripheral afferent fibres with concomitant release of excitatory amino acids and neuropeptides leads to postsynaptic changes in second-order nociceptive neurons, such as an excess of signalling due to phosphorylation of *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. These second-order changes plausibly explain physical allodynia and are reflected by enhanced sensory thalamic neuronal activity, as supported by data from animal[42] and human studies[43]. Hyperexcitability can also be caused by a loss of γ-aminobutyric acid (GABA)-releasing inhibitory interneurons that can also switch to exert consequently excitatory actions at spinal levels[44]. In addition, there are less well-understood functional changes in non-neuronal cells within the spinal cord, such as microglia and astrocytes, which contribute to the development of hypersensitivity[45].

Inhibitory modulation changes. In addition to changes in pain transmission neurons, inhibitory interneurons and descending modulatory control systems are dysfunctional in patients with neuropathic pain. Interneuron dysfunction contributes to the overall altered balance between descending inhibitions and excitations; specifically, neuropathy leads to a shift in excitation that now dominates. Consequently, the brain receives altered and abnormal sensory messages. Altered projections to the thalamus and cortex and parallel pathways to the limbic regions account for high pain ratings and anxiety, depression and sleep problems, which are relayed as painful messages that dominate limbic function.

Areas such as the cingulate cortex and amygdala have been implicated in the ongoing pain state and comorbidities associated with neuropathic pain[46]. Projections from these forebrain areas modulate descending controls running from the periaqueductal grey (the primary control centre for descending pain modulation) to the brainstem and then act on spinal signalling. Indeed, numerous studies have shown that the brainstem excitatory pathways are more important in the maintenance of the pain state than in its induction.

Noradrenergic inhibitions, mediated through α_2-adrenergic receptors in the spinal cord, are attenuated in neuropathic pain, and enhanced serotonin signalling through the 5-HT_2 and 5-HT_3 serotonin receptors becomes dominant. The noradrenergic system mediates the diffuse noxious inhibitory controls (DNICs), the animal counterpart of the human conditioned pain modulation (CPM; FIG. 3), in which one pain inhibits another through descending pathways. DNICs (and CPM) are lost or at least partially impaired in those with neuropathy. Animals that recruit noradrenergic

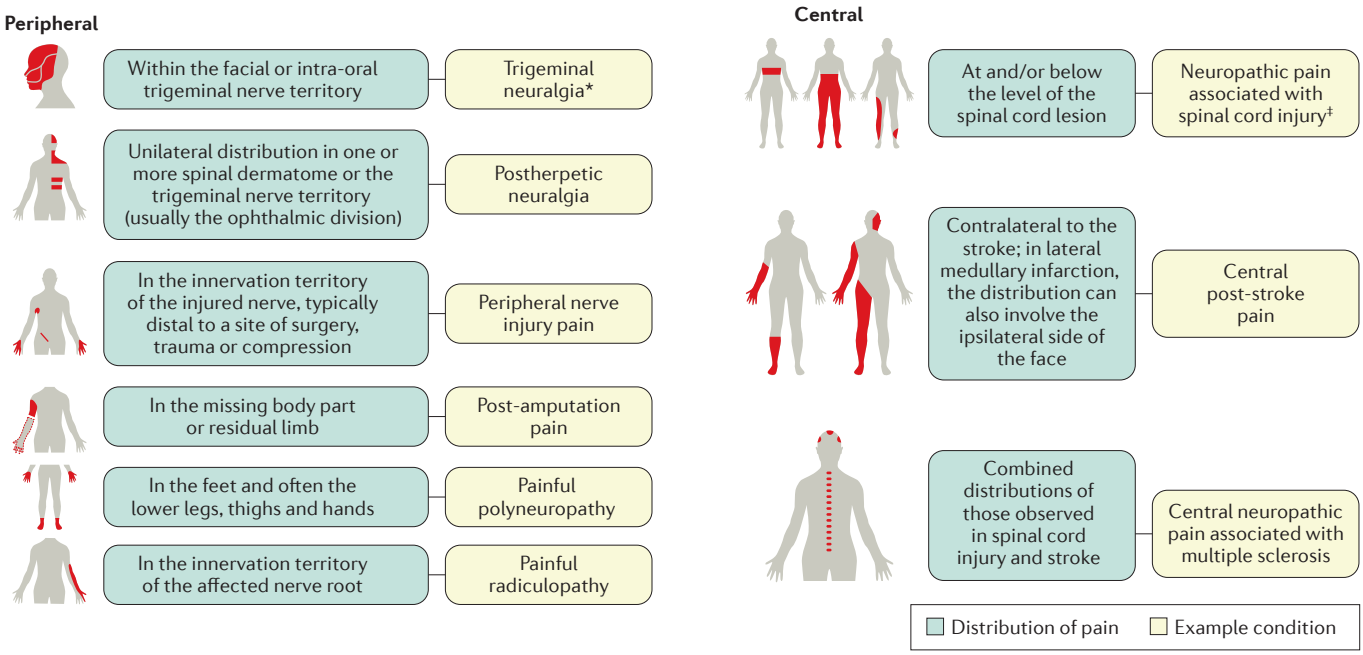

Figure 2 | **Neuroanatomical distribution of pain symptoms and sensory signs in neuropathic pain conditions.** Distribution of pain and sensory signs in common peripheral and central neuropathic pain conditions. *Can sometimes be associated with central neuropathic pain. ‡Can sometimes be associated with peripheral neuropathic pain.

inhibitions have markedly reduced hypersensitivity after neuropathy despite identical levels of nerve damage[47], explaining the advantage of using medication that manipulates the monoamine system to enhance DNICs in patients by blocking descending facilitations.

Pain modulation mechanisms

Some patients with neuropathic pain are moderately affected, whereas others experience debilitating pain. Moreover, patients show a large variability in response to distinct pharmacological (in terms of type and dose) and non-pharmacological treatments. A key factor in this variability might be the way that the pain message is modulated in the CNS. The pain signal can be augmented or reduced as it ascends from its entry port (the dorsal horn), relayed to the CNS and arrives at the cerebral cortex (the area crucial for consciousness). The various pathways and interference can, accordingly, modify the assumed correlation between the extent of the peripheral pathology and the extent of the pain syndrome. Most patients with neuropathic pain express a pro-nociceptive pain modulation profile — that is, pain messages are augmented in the CNS[48]. Thus, the perception of pain can be disinhibited owing to decreased descending endogenous inhibition, which is depicted by less-efficient CPM (BOX 1), facilitated through sensitization of ascending pain pathways, which is depicted by enhanced temporal summation of painful stimulations, or both. Temporal summation is augmented in neuropathic and non-neuropathic pain, but patients with neuropathic pain present with a higher slope of increase[48]. CPM has been shown to be less efficient in patients with various pain syndromes than in healthy controls[49].

The prospect of harnessing pain modulation seems promising for a more individualized approach to pain management. Indeed, studies have shown that the pain modulation profile can predict the development and extent of chronic postoperative pain[50–52]. If these findings are confirmed by larger studies, we can speculate that patients who express a facilitatory pro-nociceptive profile could be treated with a drug that reduces the facilitation (such as gabapentinoids) and patients who express an inhibitory pro-nociceptive profile could be treated with a drug that enhances the inhibitory capacity (for example, serotonin–noradrenaline reuptake inhibitors)[50]. Patients who express both less-efficient CPM and enhanced temporal summation might need a combination of treatments. Indeed, the level of CPM predicts the efficacy of duloxetine (a selective serotonin–noradrenaline reuptake inhibitor) in patients; CPM is restored with both duloxetine and tapentadol (a noradrenaline reuptake inhibitor). Moreover, the altered pain modulation profile of a patient can be reversed towards normality when pain is treated, as exemplified with arthroplasty surgery in patients with osteoarthritis; when the diseased joint is replaced, the majority of patients will be free of pain and the central and peripheral processes normalize[34,53,54].

Notably, pain modulation is highly influenced by expectancy-induced analgesia, in which changes due to the beliefs and desires of patients and providers[55] affect response to treatment for neuropathic pain. In laboratory settings, expectancy-induced analgesia influences clinical pain in irritable bowel syndrome[56–58], idiopathic and neuropathic pain[59]. For example, Petersen *et al.*[60,61] tested expectancy-induced analgesia in patients who developed neuropathic pain after thoracotomy. Patients received

lidocaine in an open (that is, patients were told: "The agent you have just been given is known to powerfully reduce pain in some patients") or hidden ("This is a control condition for the active medication") manner in accordance with a previously described protocol[62]; the results showed a large reduction of ongoing pain, maximum wind-up-like pain and an area of hyperalgesia in those in the open group, recapitulating previous reports[59,60]. These findings point to a clinically relevant endogenous pain inhibitory mechanism with implications for phenotyping patients with neuropathic pain in clinical trial designs and practices. Such effects should be reduced in clinical trials and intentionally enhanced in daily clinical practices as a strategy to optimize pain management.

Diagnosis, screening and prevention

A system was proposed to determine the level of certainty with which the pain in question is neuropathic as opposed, for example, to nociceptive pain[5] (FIG. 4a). If the patient's history suggests the presence of a neurological lesion or disease and the pain could be related to such (for example, using validated screening tools) and the pain distribution is neuroanatomically plausible, the pain is termed 'possible' neuropathic pain. 'Probable' neuropathic pain requires supporting evidence obtained by a clinical examination of sensory signs (for example, bedside testing and quantitative sensory testing). 'Definite' neuropathic pain requires that an objective diagnostic test confirms the lesion or disease of the somatosensory nervous system (for example, neurophysiological tests and skin biopsy). A minimum finding of probable neuropathic pain should lead to treatment.

On the basis of the assumption that characteristic qualities indicative of neuropathic pain in sensory perception are present, several screening tools have been developed to identify neuropathic pain conditions or neuropathic components to chronic pain syndromes[63] (BOX 2). These simple to use patient-reported questionnaires, for example, the DN4 or painDETECT[22,64], assess characteristic neuropathic pain symptoms (such as burning, tingling, sensitivity to touch, pain caused by light pressure, electric shock-like pain, pain to cold or heat, and numbness) and can distinguish between neuropathic and non-neuropathic pain with high specificity and sensitivity when applied in patients with chronic pain. Other tools, such as the Neuropathic Pain Symptom Inventory (NPSI)[65], have been more specifically developed for the quantification of neuropathic symptoms and dimensions and have contributed to further phenotype individual patients particularly for clinical trials.

Confirmatory tests for nerve damage

Different psychophysical and objective diagnostic tests are available to investigate somatosensory pathway function, including bedside evaluation and assessment of sensory signs as well as neurophysiological techniques, skin biopsy and corneal confocal microscopy (FIG. 4b). Of these, sensory evaluation, neurophysiological techniques and quantitative sensory testing are routinely used.

Bedside sensory assessment of sensory signs. Neuropathic pain presents as a combination of different symptoms and signs[66]. Touch, pinprick, pressure, cold, heat, vibration, temporal summation and after sensations can be examined at the bed side, whereby the patient describes the sensation after a precise and reproducible stimulus is applied[67]. To assess either a loss (negative sensory signs) or a gain (positive sensory signs) of somatosensory function, the responses are graded as normal, decreased or increased. The stimulus-evoked (positive) pain types are classified as hyperalgesic (experiencing increased pain from a stimulus that is normally perceived as less painful) or allodynic (experiencing pain from a stimulus that does not normally trigger a pain response), and according to the dynamic or static character of the stimulus.

Quantitative sensory testing. Quantitative sensory tests use standardized mechanical and thermal stimuli to test the afferent nociceptive and non-nociceptive systems in the periphery and the CNS. Quantitative sensory tests assess loss and gain of function of the entire different afferent fibre classes (Aβ, Aδ and C fibres), which is a distinct advantage over other methods[68]. The German Research Network on Neuropathic Pain[69] proposed a battery of quantitative sensory tests that consists of 13 parameters to help identify somatosensory phenotypes of patients with neuropathic pain. These thermal and mechanical tests include the determination of detection thresholds for cold, warm, paradoxical heat sensations and touch and vibration; determination of pain thresholds for cold and heat stimulations, pinprick and blunt pressure; and determination of allodynia and pain summation. Recently, normative data from a large database of healthy individuals have helped to determine gain or loss of sensory function in age-matched and sex-matched patients with neuropathic pain[70,71]. Accordingly, pathological values of positive and negative signs have been determined for most variables (FIG. 5).

Box 3 | **Neuropathic pain and diabetes mellitus**

Painful chronic neuropathy in patients with diabetes mellitus ranges from 10% to 26%[38]. Although risk factors and potential mechanisms underlying neuropathy have been studied extensively, the aetiology of the painful diabetic neuropathy is not completely known. However, findings from epidemiological studies have suggested that patients with diabetes mellitus who develop neuropathy, compared with those patients who do not, seem to have different cardiovascular function, glycaemic control, weight, rates of obesity, waist circumference, risk of peripheral arterial disease and triglyceride plasmid levels. Indeed, patients with diabetes mellitus have alterations in the peripheral and central pain pathways; other mechanistic contributors include blood glucose instability, increased peripheral nerve epineural blood flow, microcirculation of the skin of the foot, altered intraepidermal nerve fibre density, increased thalamic vascularity and autonomic dysfunction. Furthermore, methylglyoxal (a by-product of glycolysis) plasma levels are increased in patients with diabetes mellitus owing to excessive glycolysis and decreased degradation by the glyoxalase system[197]. This metabolite activates peripheral nerves by changing the function of $Na_v1.7$ and $Na_v1.8$ voltage-gated sodium channnels[197] and might, therefore, have a role in painful neuropathy. Studies in animals have shown that methylglyoxal slows nerve conduction, heightens calcitonin gene-related peptide release from nerves and leads to thermal and mechanical hyperalgesia[197]. Notably, methylglyoxal-dependent modifications of sodium channels induce diabetes-associated hyperalgesia that is not simply due to changes in peripheral fibres[197].

Neurophysiological techniques. Laser-evoked potentials (LEPs) are widely considered the most reliable neurophysiological tool to assess nociceptive functions[67,72]. For example, nerve conduction studies, trigeminal reflexes and somatosensory-evoked potentials — the Aβ fibre-mediated standard neurophysiological techniques — do not provide information on nociceptive pathways. However, they are still useful to identify damage along the somatosensory pathways and are widely used for assessing peripheral and CNS diseases that cause neuropathic pain[73]. Laser stimulations selectively activate Aδ and C nociceptors in the superficial layers of the skin[74].

LEPs related to Aδ fibre activation have been standardized for clinical application. The responses to stimulation are recorded from the scalp and consist of waveforms with different latencies. In diseases associated with damage to the nociceptive pathway, LEPs can be absent, reduced in amplitude or delayed in latency[75–77]. Among nociceptive-evoked potentials, contact heat-evoked potentials are also widely used in assessing neuropathic pain[78]. Concentric electrodes have also been introduced to measure pain-related evoked potentials and the small-fibre involvement in neuropathic pain[79]. Nevertheless, some studies suggest that concentric electrodes also activate non-nociceptive Aβ fibres; hence, pain-related evoked potential recording is not suitable for assessing nociceptive systems[78].

Skin biopsy. Skin biopsy to assess epidermal innervation is regarded as the most sensitive tool for diagnosing small-fibre neuropathies[80]. The technique is useful because the skin has widespread unmyelinated C fibre terminals, with relatively few small myelinated Aδ fibres that lose their myelin sheath and reach the epidermis as unmyelinated free nerve endings[81,82]. However, the relationship between skin biopsy data and neuropathic pain is still unclear. One study in 139 patients with peripheral neuropathy suggested that a partial sparing of intraepidermal nerve fibres, as assessed with skin biopsy, is associated with provoked pain[83].

Corneal confocal microscopy. As a non-invasive *in vivo* technique, corneal confocal microscopy can be used to quantify corneal nerve fibre damage (to small myelinated Aδ and unmyelinated C fibres) in patients with peripheral neuropathies[84,85]. However, this technique has several limitations, such as the high cost and the reduced availability in most clinical centres. Furthermore, whether some conditions (such as dry eye syndrome and Sjögren syndrome, eye diseases or previous eye surgery) influence the corneal confocal variables is still unclear[86]. No study has reliably investigated the association between corneal confocal microscopy variables and neuropathic pain.

Prevention

Given that the available treatments for neuropathic pain have meaningful but modest benefits (see Management), interventions that prevent neuropathic pain can have a substantial effect on public health. Indeed, increased attention to prevention has the potential to reduce the disability experienced by many patients with chronic neuropathic pain. Leading a healthy lifestyle and education regarding pain-causing health conditions are important components of prevention, especially in those who are at greater risk of developing neuropathic pain[87]. Prevention programmes that combine mutually reinforcing medical and behavioural interventions might lead to greater preventive benefits.

The identification of risk factors is essential to prevent neuropathic pain developing in at-risk individuals. Primary prevention strategies (in generally healthy but at-risk individuals) include the live attenuated[88,89] and subunit adjuvanted[90,91] herpes zoster vaccines, which both reduce the likelihood of developing herpes zoster infections in individuals ≥50 years of age[88–91], and therefore, reduce the likelihood of postherpetic neuralgia. Secondary prevention involves administering preventive interventions to individuals who are experiencing an illness, injury or treatment that can cause chronic neuropathic pain. Examples of this approach include the perioperative treatment of surgical patients

Box 4 | **Challenges in translating animal studies to therapeutic pharmacological targets in humans**

Translating knowledge from preclinical observations in animal models to new targeted drug therapies in the clinic has been challenging. The differences between animal behavioural tests and human neuropathic pain features, lack of long-term efficacy data in animal models and the homogeneity of animal genetic strains might contribute to these challenges. Nonetheless, a substantial part of our knowledge of neuropathic pain mechanisms is derived from animal studies. Animal models of neuropathic pain use surgical lesions of the spinal cord, cranial and peripheral sensory nerves, such as ligation, constriction or transection of parts or branches of nerves[198]. These animal models exhibit hypersensitivity to external stimuli, commonly to mechanical stimuli as assessed with von Frey hairs (for measuring the tactile sensitivity), but may also include hypersensitivity to thermal stimuli (especially cold). Higher-level outcome measurements that are suggestive of reward from pain relief and reflective of the spontaneous pain experienced by patients have recently been introduced in the array of animal models of neuropathic pain[199]. Models of diabetic neuropathy have also been affected by the ill health of the animals, but this aspect is starting to be addressed in the most recent studies[38].

Notably, basic research findings have often led to the development of specific therapeutic targets. For example, the altered function of the sodium channels within the damaged peripheral nerves provides insights into the use of topical voltage-gated sodium channel blockade (such as lidocaine[107] and carbamazepine[186]) for neuropathic pain. Moreover, the assumption of abnormal sodium channel activity has led to the use of oxcarbazepine, which has been shown to be more effective in patients with the 'irritable nociceptor' phenotype[186]. Drugs such as gabapentin and pregabalin[200] (see Management) target the $\alpha_2\delta$ subunit of the voltage-dependent calcium channels that are overexpressed in patients with neuropathic pain. When given intrathecally, gabapentin inhibited hypersensitivity in animal models[201] but has failed to show positive results in humans[202].

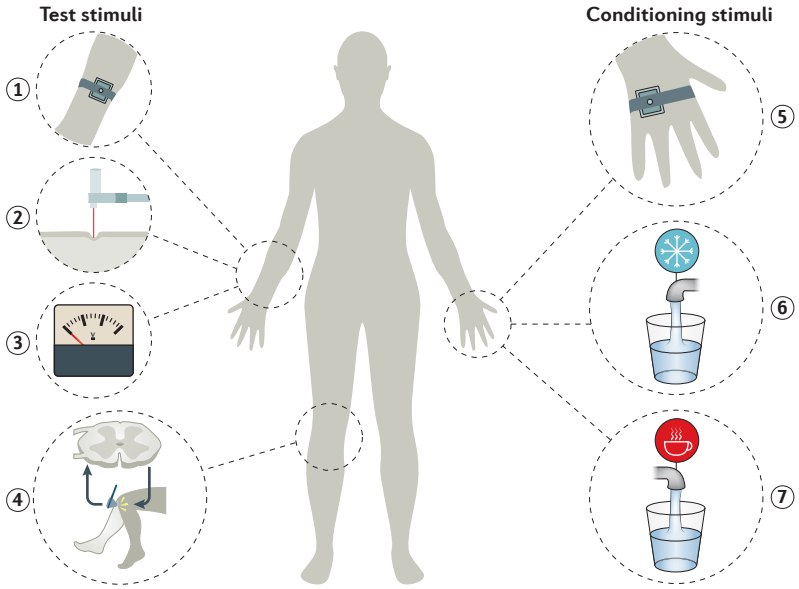

Figure 3 | **Schematic representation of the conditioned pain modulation.** The conditioned pain modulation (CPM) paradigm is used in the research setting to assess the change of perceived pain by a test stimulus under the influence of a conditioning stimulus[203]. A test stimulus can be a thermal contact stimulation (1), mechanical pressure (2), an electrical stimulus (3) — for each, either pain threshold or suprathreshold magnitude estimation can be used — or nociceptive withdrawal reflex (4). A typical conditioning stimulus consists of thermal contact stimulation (5), or immersion in a cold (6) or hot (7) water bath. Other modalities can be used as well. During a CPM assessment, a test stimulus is given first, then the conditioning stimulus is given, and the test is repeated during or immediately after the conditioning.

to prevent chronic postsurgical pain[92] and the use of antiviral or analgesic treatment in patients with herpes zoster infection[93]. Furthermore, proper management of health conditions, such as diabetes mellitus, may prevent neuropathic pain before it even presents[94].

Management

The management of neuropathic pain generally focuses on treating symptoms because the cause of the pain can be rarely treated; furthermore, the management of aetiological conditions, such as diabetes mellitus, is typically insufficient to relieve neuropathic pain. Patients with neuropathic pain generally do not respond to analgesics such as acetaminophen, NSAIDs or weak opioids such as codeine. The traditional approach to the management of a patient with neuropathic pain is to initiate treatment with conservative pharmacological and complementary therapies before interventional strategies, such as nerve blocks and neuromodulation, are used. However, the limited efficacy of the drugs, the ageing population of patients, polypharmacy in elderly patients and opioid-related adverse effects have resulted in an increasing use of interventional therapies. Clinical studies are lacking to help guide the physician in the optimal sequence of therapy in a given patient.

Medical intervention

Numerous therapeutic recommendations, with different classes of drug, for neuropathic pain have been proposed[95–99]. On the basis of a systematic review and meta-analysis of all drug studies reported on since 1966, including unpublished trials[100], pregabalin (a GABA analogue), gabapentin (a GABA inhibitor), duloxetine (a serotonin–noradrenaline reuptake inhibitor) and various tricyclic antidepressants have strong recommendations for use and are recommended as first-line treatments for peripheral and central neuropathic pain. High-concentration capsaicin (the active component of chili peppers) patches, lidocaine patches and tramadol (an opioid with serotonin and noradrenaline reuptake inhibition effects) have weak evidence in support of their use and are recommended as second-line treatments for peripheral neuropathic pain only. Strong opioids and botulinum toxin A (administered by specialists) have weak recommendations for use as third-line treatments. However, most of these treatments have moderate efficacy based on the number needed to treat (NNT; that is, the number of patients necessary to treat to obtain one responder more than the comparison treatment, typically placebo) for obtaining 50% of pain relief[101] (TABLE 1). Furthermore, pharmacological treatments for chronic neuropathic pain are effective in <50% of patients and may be associated with adverse effects that limit their clinical utility[101].

First-line treatments. Antidepressants and antiepileptics have been the most studied drugs in neuropathic pain. Among antidepressants, tricyclic antidepressants, such as amitriptyline, and serotonin–noradrenaline reuptake inhibitors, such as duloxetine, have confirmed efficacy in various neuropathic pain conditions. Their analgesic efficacy seems largely mediated by their action on descending modulatory inhibitory controls, but other mechanisms have been proposed (including an action on β_2 adrenoceptors)[102]. Among antiepileptics, the efficacy of pregabalin and gabapentin, including extended-release formulations, is best established for the treatment of peripheral neuropathic pain and, to a lesser extent, spinal cord injury pain. However, the number of negative trials has increased over the past 5 years. The analgesic effects of these drugs are mainly related to a decrease in central sensitization through binding to the $\alpha_2\delta$ subunit of calcium voltage-gated channels[103].

Combination of pregabalin or gabapentin with a tricyclic antidepressant or opioid at lower doses has resulted in beneficial effects as compared to monotherapy in peripheral neuropathic pain[100,101,104]. However, the efficacy and adverse effects of high-dose monotherapy were similar to those of moderate-dose combination therapy in patients with diabetic neuropathic pain who did not respond to monotherapy at moderate doses[105]. These studies provide a rationale for the use of combinations of drugs, at moderate dosages, in patients who are unable to tolerate high-dose monotherapy.

Second-line treatments. Lidocaine is thought to act on ectopic neuronal discharges through its sodium channel-blocking properties. The efficacy of lidocaine 5% patches has been assessed in focal peripheral postherpetic neuralgia, but their therapeutic gain is modest compared with placebo[106,107]. Capsaicin initially activates transient receptor potential cation channel subfamily V

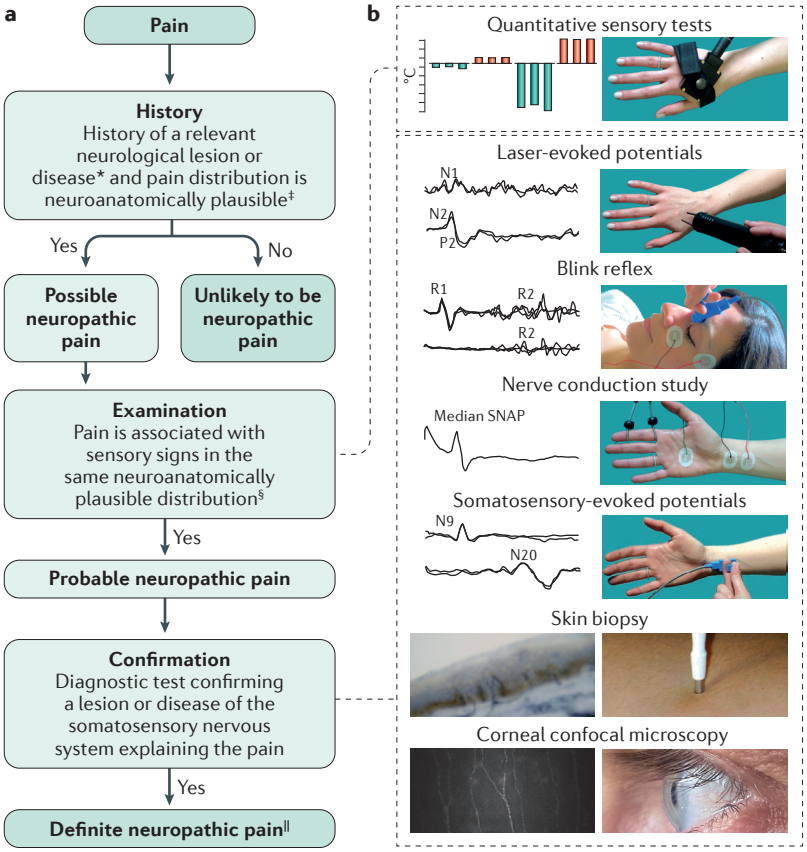

Figure 4 | **Diagnosing neuropathic pain. a** | The flowchart summarizes the clinical steps in diagnosing neuropathic pain, which involves taking the patient history, examining the patient and following up with confirmatory tests. If the answer is 'no' after examination, the patient might still have probable neuropathic pain. In such cases, confirmation tests could be performed if sensory abnormalities are not found; for example, in some hereditary conditions, sensory abnormalities are not found at the moment of examination. *History of a neurological lesion or disease relevant to the occurrence of neuropathic pain. ‡The patient's pain distribution reflects the suspected lesion or disease. §Signs of sensory loss are generally required. However, touch-evoked or thermal allodynia might be the only finding at bedside examination. ‖'Definite' neuropathic pain refers to a pain that is compatible with the features of neuropathic pain and confirmatory tests are consistent with the location and nature of the lesion or disease, although this may not imply any causality. **b** | The confirmatory tests for neuropathic pain include quantitative sensory testing (in which the patient provides a subjective report on a precise and reproducible stimulus), blink reflex testing (whereby the trigeminal afferent system is investigated by recording the R1 and R2 reflex responses recorded from the orbicularis oculi muscle) and nerve conduction study (which assesses non-nociceptive fibre function of the peripheral nerves). Somatosensory-evoked potentials (N9 is generated by the brachial plexus and N20 by the somatosensory cortex) and laser-evoked potentials (LEPs), both recorded from the scalp, are neurophysiological tools that investigate large and small afferent fibre function. The N1 LEP wave is a lateralized component and generated by the secondary somatosensory cortex, and the negative–positive complex of LEP (N2–P2) is a vertex recorded potential, which is generated by the insular cortex bilaterally and the cingulate cortex[204]. A skin biopsy enables the quantification of the intraepidermal nerve fibres, which provides a measure of small-fibre loss[77]. Finally, corneal confocal microscopy assesses corneal innervation, which consists of small nerve fibres. In most patients with neuropathic pain, standard neurophysiological testing, such as blink reflex, nerve conduction study and somatosensory-evoked potentials, is sufficient for showing the damage of the somatosensory system. However, in patients with selective damage of the nociceptive system, a nociceptive-specific tool, such as LEPs, skin biopsy or corneal confocal microscopy, is needed. Typically, tests are performed in the sequence of increasing invasiveness; that is, quantitative sensory testing, blink reflex, nerve conduction study, somatosensory-evoked potentials, LEPs, skin biopsy and corneal confocal microscopy. SNAP, sensory nerve action potential. Adapted with permission from REF. 77, Macmillan Publishers Limited. The corneal innervation image in part **b** (left panel) is reproduced with permission from REF. 86, Elsevier.

member 1 (TRPV1) ligand-gated channels on nociceptive fibres, leading to TRPV1 desensitization and defunctionalization. The sustained efficacy of a single application of a high-concentration capsaicin patch (8%) has been reported in postherpetic neuralgia[108], as well as diabetic[104] and non-diabetic painful neuropathies[109]. The long-term safety of repeated applications seems favourable based on open studies, but there are no long-term data on the effects on epidermal nerve fibres in patients with neuropathic pain[101]. Tramadol, an opioid agonist and serotonin–noradrenaline reuptake inhibitor, has also been shown to be effective, mainly in peripheral neuropathic pain; its efficacy is less established in central neuropathic pain[101].

Third-line treatments. Botulinum toxin A is a potent neurotoxin commonly used for the treatment of focal muscle hyperactivity and has shown efficacy of repeated administrations over 6 months, with enhanced effects of the second injection[110]. The toxin has a beneficial role in the treatment of peripheral neuropathic pain (for example, diabetic neuropathic pain, postherpetic neuralgia and trigeminal neuralgia)[110–112].

Opioid agonists, such as oxycodone and morphine, are mildly effective[101], but there is concern about prescription opioid-associated overdose, death, diversion, misuse and morbidity[113].

There are weak, negative or inconclusive recommendations for the use of all other drug treatments for neuropathic pain in general. Antiepileptics other than $\alpha_2\delta$ ligands (for example, topiramate, oxcarbazepine, carbamazepine, valproate, zonisamide, lacosamide and levetiracetam) fall into these categories, although some agents are probably effective in subgroups of patients. Oromucosal cannabinoids have been found to be variably effective in pain associated with multiple sclerosis and in peripheral neuropathic pain with allodynia, but several unpublished trials were negative on the primary outcome. Results for selective serotonin reuptake inhibitors, NMDA antagonists, mexiletine (a non-selective voltage-gated sodium channel blocker) and topical clonidine (an α_2-adrenergic agonist and imidazoline receptor agonist) have generally been inconsistent or negative except in certain subgroups.

Emerging treatments. A few drugs targeting novel mechanisms of action are under clinical development for the treatment of peripheral neuropathic pain. These include, in particular, subtype selective sodium channel-blocking agents, particularly $Na_v1.7$ antagonists[114], and EMA401, a novel angiotensin type II antagonist that has been found to be effective in a phase II clinical trial in postherpetic neuralgia[115]. Although still in the preclinical phase, studies show promising results of stem cell treatment for neuropathic pain[116,117].

Interventional therapies

Interventional treatments, such as nerve blocks or surgical procedures that deliver drugs to targeted areas, or modulation of specific neural structures, provide alternative treatment strategies in selected patients

with refractory neuropathic pain[118,119] (FIG. 6). Although generally safe (see below), spinal cord stimulation and peripheral nerve stimulation have been associated with hardware-related, biological complications, such as infections and programming-related or treatment-related adverse effects (including painful paraesthesias)[120,121].

Neural blockade and steroid injections. A perineural injection of steroids provides transient relief (1–3 months) for trauma-related and compression-related peripheral neuropathic pain[122]. Systematic reviews and meta-analysis of epidural steroid injections for the treatment of cervical and lumbar radiculopathies indicate an immediate modest reduction in pain and function of <3 months duration, but had no effects on reducing the risk for subsequent surgery[119,123,124]. Epidural local anaesthetic and steroid nerve blocks were given a weak recommendation for the treatment of lumbar radiculopathy and acute zoster-associated neuropathic pain[119]. Although sympathetic ganglion blocks have been used to treat pain in some patients with complex regional pain syndromes (also known as causalgia and reflex sympathetic dystrophy), the evidence for long-term benefit is weak[119].

Spinal cord stimulation. Low-intensity electrical stimulation of large myelinated Aβ fibres was introduced based on the gate control theory[125] as a strategy to modulate the pain signals transmitted by the unmyelinated C fibres. The most commonly used and the best-studied neuromodulation strategy has been spinal cord stimulation, in which a monophasic square-wave pulse (frequency ranging 30–100 Hz) is applied, resulting in paraesthesia in the painful region[126]. Newer stimulation parameters, such as burst (40 Hz burst with five spikes at 500 Hz per burst) and high-frequency (10 kHz with sinusoidal waveforms) spinal cord stimulation, provide paraesthesia-free stimulation and equivalent or better pain relief compared with the monophasic square-wave pulse[127,128].

The relative safety and reversibility of spinal cord stimulation, as well as its cost-effectiveness over the long term have made it an attractive strategy for managing patients with refractory chronic neuropathic pain[129–131]. Systematic reviews, randomized controlled trials and several case series provide evidence for the long-term efficacy of spinal cord stimulation when combined with medical treatment compared with medical management in various pain neuropathies[132–134], and has been shown to offer sustained results at 24 months of treatment[135,136]. Two randomized trials in individuals with painful diabetic neuropathy reported greater reduction in pain and improvements in measures of quality of life compared with controls[137,138]. Current European guidelines provide a weak recommendation for spinal cord stimulation (combined with medical treatment) in, for example, diabetic neuropathic

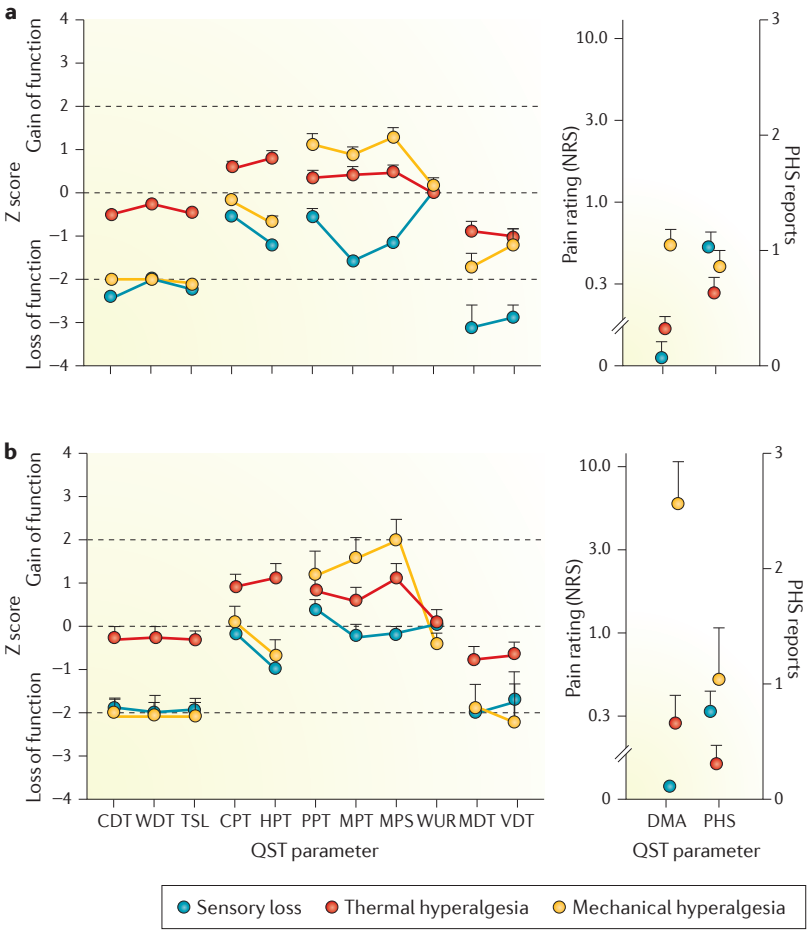

Figure 5 | **Subgrouping patients with peripheral neuropathic pain based on sensory signs.** On the basis of two well-established testing ($n = 902$) (part **a**) and control ($n = 233$) (part **b**) data sets[69], three categories of patient phenotypes for neuropathic pain have been proposed: sensory loss, thermal hyperalgesia and mechanical hyperalgesia. Positive scores indicate positive sensory signs (hyperalgesia), and negative scores indicate negative sensory signs (hypoaesthesia or hypoalgesia). Values observed in those with neuropathic pain are significantly different from those of healthy participants when the 95% CI does not cross the zero line, which defines the average of data from normal subjects. Insets (right) show the numerical rating scale (NRS; 0–10) values for dynamic mechanical allodynia (DMA) on a logarithmic scale and the frequency of paradoxical heat sensation (PHS) on a scale of 0–3. These findings indicate that patients with neuropathic pain have different expression patterns of sensory signs. These subgroup results suggest that different mechanisms of pain generation are involved in the pain condition. Furthermore, the first clinical trial to show phenotype stratification based on these sensory profiles has predictive power for treatment response[186]. Error bars are the graphical representation of the variability of the data present in the database. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; QST, quantitative sensory test; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio. Reproduced with permission from REF. 70, Baron, R. *et al.*, Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles, *Pain*, **158**, 2, 261–272, http://journals.lww.com/pain/Fulltext/2017/02000/Peripheral_neuropathic_pain___a_mechanism_related.10.aspx

pain[118,119,139]. The success of spinal cord stimulation for neuropathic pain may depend on the appropriate selection of patients based on psychological traits, sensory phenotype, enhanced central sensitization and reduced CPM[140,141].

Dorsal root ganglion, peripheral nerve and peripheral nerve field stimulation. Neurostimulation of afferent fibres outside the spinal cord (for example, the dorsal root ganglion, which contains the cell bodies of sensory neurons, and peripheral nerves) and subcutaneous peripheral nerve field stimulation have been reported to provide pain relief in various chronic neuropathic pain states, including occipital neuralgia and postherpetic neuralgia[142,143]. A multicentre prospective cohort study in patients with chronic neuropathic pain reported that dorsal root ganglion stimulation provided 56% pain reduction with a 60% responder rate (>50% reduction in pain)[144]. These preliminary observations are being examined with controlled trials.

Epidural and transcranial cortical neurostimulation. Epidural motor cortex stimulation (ECMS), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) of the precentral motor cortex at levels below the motor threshold have been proposed as treatment options for patients with refractory chronic neuropathic pain[145–147]. Cortical neurostimulation may reduce pain-related thalamic hyperactivity or activate descending inhibitory pathways. Meta-analysis reports suggest that 60–65% of patients respond (>40% pain reduction) to EMCS[147]. ECMS is a neurosurgical procedure that requires precise intra-operative placement of the stimulating electrode

Table 1 | **Available pharmacotherapy for neuropathic pain**

Drug	Mechanisms of action	NNT* (range)	Adverse effects	Precautions and contraindications
Tricyclic antidepressants				
Nortriptyline, desipramine, amitriptyline, clomipramine and imipramine	Monoamine reuptake inhibition, sodium channel blockade and anticholinergic effects	3.6 (3–4.4)	Somnolence, anticholinergic effects and weight gain	• Cardiac disease, glaucoma, prostatic adenoma and seizure • High doses should be avoided in adults >65 years of age and in those with amyloidosis
Serotonin–noradrenaline reuptake inhibitors				
Duloxetine	Serotonin and noradrenaline reuptake inhibition	6.4 (5.2–8.2)	Nausea, abdominal pain and constipation	• Hepatic disorder and hypertension • Use of tramadol
Venlafaxine	Serotonin and noradrenaline reuptake inhibition	6.4 (5.2–8.2)	Nausea and hypertension at high doses	• Cardiac disease and hypertension • Use of tramadol
Calcium channel $\alpha_2\delta$ ligands				
Gabapentin, extended-released gabapentin and enacarbil, and pregabalin	Act on the $\alpha_2\delta$ subunit of voltage-gated calcium channels, which decrease central sensitization	• 6.3 (5–8.4 for gabapentin) • 8.3 (6.2–13 for extended-released gabapentin and enacarbil) • 7.7 (6.5–9.4 for pregabalin)	Sedation, dizziness, peripheral oedema and weight gain	Reduce dose in patients with renal insufficiency
Topical lidocaine				
Lidocaine 5% plaster	Sodium channel blockade	Not reported	Local erythema, itching and rash	None
Capsaicin high-concentration patch (8%)	Transient receptor potential cation channel subfamily V member 1 agonist	10.6 (7.4–19)	Pain, erythema, itching and rare cases of high blood pressure (initial increase in pain)	No overall impairment of sensory evaluation after repeated applications and caution should be taken in progressive neuropathy
Opioids				
Tramadol	μ-Receptor agonist and monoamine reuptake inhibition	4.7 (3.6–6.7)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk and use of antidepressant in elderly patients
Morphine and oxycodone	μ-Opioid receptor agonists; oxycodone might also cause κ-opioid receptor antagonism	4.3 (3.4–5.8)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk and risk of misuse in the long term
Neurotoxin				
Botulinum toxin A	Acetylcholine release inhibitor and neuromuscular-blocking agent; potential effects on mechanotransduction and central effects in neuropathic pain	1.9 (1.5–2.4)	Pain at injection site	Known hypersensitivity and infection of the painful area

*Number needed to treat (NNT) for 50% pain relief represents the number of patients necessary to treat to obtain one responder more than the comparison treatment, typically placebo[101].

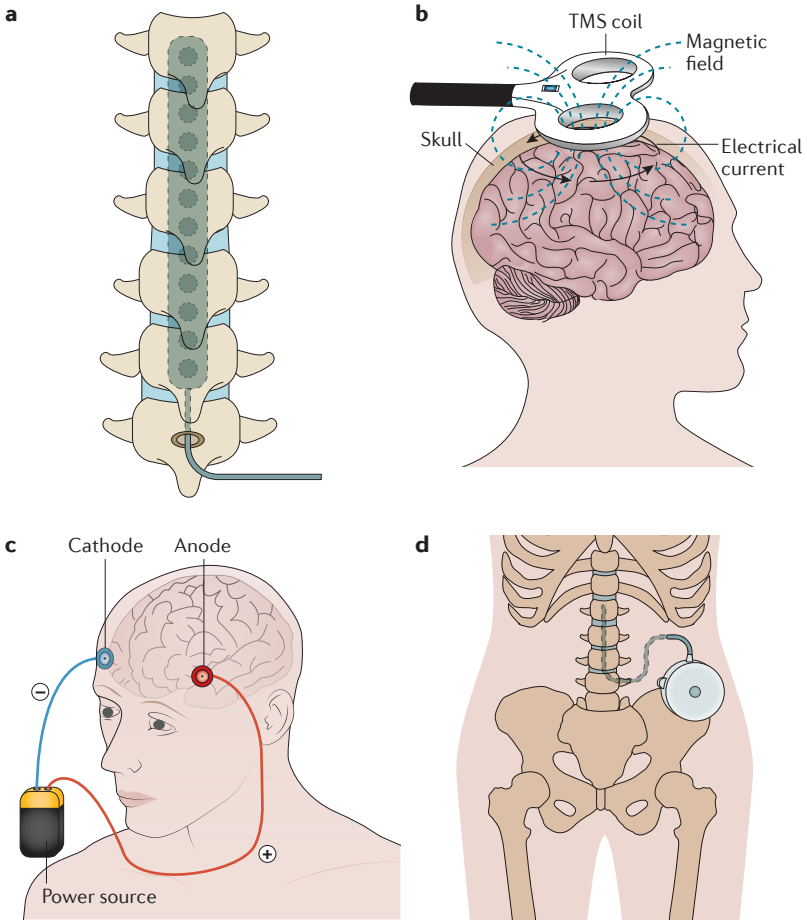

Figure 6 | **Example interventional treatments for neuropathic pain. a** | Spinal cord stimulation traditionally applies a monophasic square-wave pulse (at a frequency in the 30–100 Hz range) that results in paraesthesia in the painful region. **b** | Cortical stimulation involves the stimulation of the pre-central motor cortex below the motor threshold using either invasive epidural or transcranial non-invasive techniques (such as repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation). **c** | Deep brain stimulation uses high-frequency chronic intracranial stimulation of the internal capsule, various nuclei in the sensory thalamus, periaqueductal and periventricular grey, motor cortex, septum, nucleus accumbens, posterior hypothalamus and anterior cingulate cortex as potential brain targets for pain control. **d** | Intrathecal treatments provide a targeted drug delivery option in patients with severe and otherwise refractory chronic pain. The pumps can be refilled through an opening at the skin surface.

over the motor cortex region corresponding to the painful body part for optimal outcome.

rTMS and tDCS are non-invasive therapies that involve neurostimulation of brain areas of interest via magnetic coils or electrodes on the scalp. Repetitive sessions (5–10 sessions over 1–2 weeks) with high-frequency rTMS (5–20 Hz) have shown benefits in a mixture of central, peripheral and facial neuropathic pain states, with effects lasting >2 weeks after the stimulation. tDCS has been reported to be beneficial in reducing several peripheral neuropathic conditions[148]. Current European guidelines include a weak recommendation for the use of EMCS and rTMS in refractory chronic neuropathic pain and tDCS for peripheral neuropathic pain[133]. Contraindications of rTMS include a history of epilepsy and the presence of aneurysm clips, deep brain electrodes, cardiac pacemakers and cochlear implants.

Deep brain stimulation. The use of long-term intracranial stimulation for neuropathic pain remains controversial. Multiple sites for deep brain stimulation, including the internal capsule, various nuclei in the sensory thalamus, periaqueductal and periventricular grey, motor cortex, septum, nucleus accumbens, posterior hypothalamus and anterior cingulate cortex, have been examined as potential brain targets for pain control[149]. The UK National Institute for Health and Care Excellence (NICE) guidelines recognize that the procedure can be efficacious in some patients who are refractory to other forms of pain control, but current evidence on the safety of deep brain stimulation shows significant potential risks, such as intra-operative seizure, lead fractures and wound infections[98]. Contrary to the NICE guidelines, the current European guidelines give inconclusive recommendations[139].

Intrathecal therapies. Intrathecal therapies have been developed to deliver drugs to targeted nerves through an implanted and refillable pump in patients with severe and chronic pain that is refractory to conservative treatments, including psychological, physical, pharmacological and neuromodulation therapies[150,151]. The report from the 2012 Polyanalgesic Consensus Conference highlighted that this therapy is associated with risks of serious morbidity and mortality and made recommendations to reduce the incidence of these serious adverse effects[152]. The only US FDA-approved drugs for use with such devices are morphine and ziconotide (an N-type calcium channel antagonist)[153]. The most frequently reported adverse reactions associated with intrathecal ziconotide are dizziness, nausea, confusion, memory impairment, nystagmus (uncontrolled movement of the eyes) and an increase in the levels of serum creatine kinase. Ziconotide is contraindicated in patients with a history of psychosis, and patients should be monitored for evidence of cognitive impairment, hallucinations or changes in mood and consciousness. No high-quality randomized trials have been conducted to assess the efficacy of ziconotide and morphine; hence, the recommendations are a consensus of experts based on clinical experience or case series.

Physical therapies

Physical therapy, exercise and movement representation techniques (that is, treatments such as mirror therapy and motor imagery that use the observation and/or imagination of normal pain-free movements) have been suggested to be beneficial in neuropathic pain management[154,155]. For example, mirror therapy and motor imagery are effective in the treatment of pain and disability associated with complex regional pain syndrome type I and type II[156]. The quality of evidence supporting these interventions for neuropathic pain is weak and needs further investigation[154,157].

Psychological therapies

People with chronic pain are not passive; they actively attempt to change the causes of pain and change their own behaviour in response to pain. However, for many

patients, such change without therapeutic help is unachievable, and repeated misdirected attempts to solve the problem of pain drive them further into a cycle of pain, depression and disability[158]. At present, there is no evidence for identifying who is at risk of untreatable, difficult to manage neuropathic pain and who might benefit from psychological intervention, although research is underway on the former[159].

Psychological interventions are designed to promote the management of pain and to reduce its adverse consequences. Treatments are often provided after pharmacological or physical interventions have failed, although they could be introduced earlier and in concert with non-psychological interventions. Cognitive–behavioural therapy (CBT) has received the most research attention; however, CBT is not a single treatment and can be usefully thought of as a family of techniques that are woven together by a clinical narrative of 'individual change' delivered by therapists who actively manage treatment. Such treatments address mood (typically anxiety and depression), function (including disability) and social engagement, as well as indirectly targeting analgesia. Secondary outcomes are sometimes reported because they are deemed important to treatment delivery (for example, therapeutic alliance and self-efficacy) or because they are valued by one or more stakeholder (for example, return to work and analgesic use).

A *Cochrane* systematic review of psychological interventions for chronic pain analysed data from 35 trials, which showed small-to-moderate effects of CBT over comparisons such as education, relaxation and treatment as usual[160]. In a companion review of 15 trials delivering treatment via the Internet, a similar broadly positive conclusion emerged, although the confidence in the estimates of effects was low[161]. Psychological treatments other than behavioural therapy and CBT were considered in this review, but none was of sufficient quality to include. Another *Cochrane* review of trials specifically undertaken in patients with neuropathic pain found no evidence for or against the efficacy and safety of psychological interventions for chronic neuropathic pain[162], which is not surprising given the similar findings for non-psychological interventions[163]. An urgent need for studies of treatments that are designed specifically for patients with neuropathic pain exists, in particular, those with painful diabetic neuropathy, which is a growing problem[164]. Specifically, studies of CBT are needed with content that is specifically designed to meet the psychosocial needs of patients with neuropathy, in particular, with regard to the multiple sensory challenge, comorbidity and polypharmacy[165]. A recognition that neuropathic pain increases with age will also mean that an understanding of later-life accommodation to illness will be important[166]. In addition, a methodological focus on individual experience and trajectories of change is needed, either through single case experiments or through ecological momentary assessment[167]. Furthermore, communication technology, in particular, the use of mobile health innovation, is likely to play an important part in future solutions. However, how to manage effective therapeutic relationships at a distance, and how technology can augment and improve face-to-face CBT remain to be clarified[168]. Technical psychological variables — such as catastrophic thinking, acceptance or readiness to change — should be relegated to process variables. Conversely, a pragmatic focus on patient-reported outcomes will be essential to reduce pain, improve mood and reduce disability, which will ultimately improve quality of life.

Quality of life

Neuropathic pain can substantially impair quality of life as it often associates with other problems, such as loss of function, anxiety, depression, disturbed sleep and impaired cognition. Measures of health-related quality of life (HRQOL) that capture broad dimensions of health including physical, mental, emotional and social functioning are increasingly used when assessing the efficacy of different interventions to manage chronic neuropathic and non-neuropathic pain. It is mainly useful when calculating quality-adjusted life years, which are necessary for cost-utility analyses.

The most commonly used HRQOL instruments are general, whereas others have been designed specifically for those with neuropathic pain. Meyer-Rosberg and colleagues validated both the 36-Item Short Form Health Survey (SF-36) and the Nottingham Health Profile (NHP) in the assessment of HRQOL in neuropathic pain related to peripheral nerve or nerve root lesions in patients attending multidisciplinary pain clinics[169]. The scores of all eight dimensions (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health) in the SF-36 were significantly lower in those with neuropathic pain than in the general population, which is in line with another study[170].

The onset of neuropathy in patients with diabetes mellitus has been shown to significantly decrease all aspects of quality of life[171]. If diabetic polyneuropathy is accompanied by pain, both physical and mental components of quality of life are further affected[172]. A recent study also showed that both EuroQol five dimensions (EQ-5D) and Short Form-6 dimension (SF-6D) questionnaires can discriminate between chronic pain with or without neuropathic pain[173]. Furthermore, the role of psychological factors in impairing quality of life in neuropathic pain has been analysed[174], showing, for example, that pain catastrophizing was associated with decreased HRQOL[174]. The SF-36 and the EQ-5D have been the most commonly used instruments in clinical trials to assess the efficacy of treatments, such as gabapentin in postherpetic neuralgia[175], diabetic polyneuropathy[176] and neuropathic pain due to peripheral nerve injury[170]; the efficacy of duloxetine in diabetic peripheral neuropathy[177]; and the efficacy of spinal cord stimulation in diabetic polyneuropathy[178].

Outlook

Although nervous system mechanisms underlying chronic neuropathic pain have been uncovered through animal and human research, the development of novel interventions with improved efficacy and tolerability has been slow. New therapeutic approaches

as well as improved clinical trial designs, specifically addressing genotypic and phenotypic profiles, have great promise to build on recent advances in basic and translational research.

Clinical trial design

The explanations for the slow progress in identifying treatments with improved efficacy that are receiving the greatest attention are inadequate clinical trial assay sensitivity and the need to target treatment to patients who are most likely to respond[179,180]. Assay sensitivity refers to the ability of a clinical trial to distinguish an efficacious treatment from placebo (or another comparator). The possibility that recent neuropathic pain clinical trials suffer from limited assay sensitivity is consistent with the observation that a considerable number of recent trials in patients with neuropathic pain investigating medications with well-established efficacy have returned negative results[7,181]. For example, a recent analysis of neuropathic pain trials showed that assay sensitivity was compromised by including patients with highly variable baseline pain ratings[182], which suggests that trials might have greater assay sensitivity if highly variable baseline pain ratings were an exclusion criterion[115].

The outcomes of clinical trials in neuropathic pain have generally shown modest efficacy, with the NNTs for 50% pain relief ranging from six to eight for positive studies in the latest meta-analysis[101]. Several reasons could account for these results[179,181], including high placebo responses, variability in the diagnostic criteria used for neuropathic pain in clinical trials and limited assay sensitivity. Thus, it has been proposed that an alternative therapeutic approach to neuropathic pain should incorporate stratification of patients according to clinical phenotypes (signs and symptoms)[66,77,183,184], whereas most trials have simply classified patients according to aetiology.

Phenotyping

Several clinical trials provide support for the relevance of phenotypic subgrouping of patients, which has the potential to lead to a more personalized pain therapy in the future[107,110,185,186]. In particular, two phenotypes — the presence of mechanical allodynia and preserved nociceptive function — are often combined and seem to predict the response to systemic and topical sodium channel blockers, botulinum toxin A and clonidine gel in recent clinical trials[107,110,185]. Indeed, any personalized pain treatments will rely on the ability to select patients who are likely to respond[187].

The strongest evidence showing that profiles of signs and symptoms can identify treatment responders stems from a trial in which patients who were defined as having an irritable nociceptor phenotype experienced a greater decrease in pain with oxcarbazepine versus placebo than those without this phenotype[186]. This is the only trial in which a pre-specified primary analysis demonstrated a difference in treatment versus placebo response in patient subgroups identified by phenotyping. These results are very promising, but require replication as well as use of phenotyping measures that would be suitable for larger confirmatory trials and use in clinical practice[188]. Phenotyping could also be used to test whether certain patients have a more robust response to non-pharmacological treatments, for example, invasive, psychological and complementary interventions[188], as well as to identify which patients are most likely to respond to combinations of treatments. Indeed, given the importance of expectations and psychological and social factors — including adaptive coping and catastrophizing — in the development and maintenance of chronic neuropathic pain, it would not be surprising if phenotyping has a great part to play in demonstrating the efficacy of psychological interventions as it does for medications.

To advance the design, execution, analysis and interpretation of clinical trials of pain treatments, several public–private partnerships have undertaken systematic efforts to increase assay sensitivity and provide validated approaches for phenotyping patients and identifying those who are most likely to respond to treatment. These efforts — which include ACTTION (www.acttion.org), EuroPain (www.imieuropain.org) and the German Research Network on Neuropathic Pain (www.neuro.med.tu-muenchen.de/dfns/) — are providing an evidence base for the design of future neuropathic pain clinical trials and for the development of mechanism-based approaches to personalized neuropathic pain treatment.

Personalized pain medicine

Personalized medical care refers to the principle that patients can be stratified such that each patient receives the most effective and tolerable treatment for their individual needs. Patients can be stratified on several levels: clinical phenotype, detailed sensory profiling, genetics and potentially (in the future) using cellular models to facilitate treatment choice. Close consultation with the patient is required and this involves complex discussions around the uncertainties of genetic risk and the balance between efficacy and tolerability of potential treatments. Human genetics studies have demonstrated that $Na_v1.7$ is a crucial pain target[189], and therapeutics aimed at targeting $Na_v1.7$ provide an example of a situation in which testing for specific genetic mutations can inform patient care. Loss-of-function mutations lead to congenital insensitivity to pain and gain-of-function mutations cause rare inherited pain disorders, including inherited erythromelalgia[31], paroxysmal extreme pain disorder[32] and idiopathic small-fibre neuropathy (which involves pain and small-fibre degeneration in the extremities)[33].

Genetic information can, therefore, inform diagnostics; however, the interpretation of genetic results is complex and should be accompanied by functional analysis of mutant ion channels wherever possible[190]. For instance, in the context of small-fibre neuropathy, mutations might not be fully penetrant. Finding a mutation in *SCN9A* may have immediate implications for treatment in choosing a drug with activity against voltage-gated sodium channels (not normally first-line agents in the

treatment of neuropathic pain), such as mexiletine, which is not recommended in the treatment of neuropathic pain but is used in inherited erythromelalgia, in which mexiletine has proven efficacy in normalizing abnormal channel properties *in vitro*[191] and clinical efficacy in individual cases. A further step has been taken in using structural modelling of $Na_v1.7$ to predict what treatment a specific mutation will respond to[192]; the modelling results were used to predict the efficacy of carbamazepine (a voltage-gated sodium channel blocker) in inherited erythromelalgia associated with the *SCN9A* S241T mutation[193]. Furthermore, the generation of nociceptors *in vitro* using patient-derived induced pluripotent stem cells is now possible. In rare Mendelian pain disorders (such as inherited erythromelalgia), these nociceptors have been shown to be hyperexcitable[194]. Treatments targeting $Na_v1.7$ can be screened in such cellular models and related to clinical efficacy as proof of concept before their use in patients (these nociceptors have been shown to be hyperexcitable in inherited erythromelalgia[194]).

Genetic stratification is more challenging in common acquired neuropathic pain states, such as painful diabetic neuropathy, because such conditions are polygenic and subject to considerable environmental interaction. Thus, the relevance of an individual target such as $Na_v1.7$ in these conditions is less clear. Despite these limitations, the prospect of personalized medicine is a step forward towards promising pain management strategies.

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Competing interests
L.C. has received lecture honoraria (Georgetown University and Stanford University) and has acted as speaker or consultant for Grünenthal and Emmi Solution. R.B. is an industry member of AstraZeneca, Pfizer, Esteve, UCB Pharma, Sanofi Aventis, Grünenthal, Eli Lilly and Boehringer Ingelheim; has received lecture honoraria from Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai, Lilly, Boehringer Ingelheim, Astellas, Desitin, Teva Pharma, Bayer-Schering, MSD and Seqirus; and has served as a consultant for Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai, Lilly, Boehringer Ingelheim Pharma, Astellas, Desitin, Teva Pharma, Bayer-Schering, MSD, Novartis, Bristol-Myers Squibb, Biogen idec, AstraZeneca, Merck, AbbVie, Daiichi Sankyo, Glenmark Pharmaceuticals, Seqirus, Genentech, Galapagos NV and Kyowa Hakko Kirin. A.H.D. has acted as speaker or consultant forSeqirus, Grünenthal, Allergan and Mundipharma. D.B. has acted as a consultant for Grünenthal, Pfizer and Indivior. D.L.B. has acted as a consultant for Abide, Eli Lilly, Mundipharma, Pfizer and Teva. D.Y. received a lecture honorarium from Pfizer and holds equity in BrainsGate and Theranica. R.F. has acted as an advisory board member for Abide, Astellas, Biogen, Glenmark, Hydra, Novartis and Pfizer. A.T. has received research funding, lecture honoraria and acted as speaker or consultant for Mundipharma, Pfizer, Grünenthal and Angelini Pharma. N.A. has received honoraria for participation in advisory boards or speaker bureau by Astellas, Teva, Mundipharma, Johnson and Johnson, Novartis and Sanofi Pasteur MSD. N.B.F. has received honoraria for participation in advisory boards from Teva Pharmaceuticals, Novartis and Grünenthal, and research support from EUROPAIN Investigational Medicines Initiative (IMI). E.K. has served on the advisory boards of Orion Pharma and Grünenthal, and received lecture honoraria from Orion Pharma and AstraZeneca. R.H.D. has received research grants and contracts from the US FDA and the US NIH, and compensation for activities involving clinical trial research methods from Abide, Aptinyx, Astellas, Boston Scientific, Centrexion, Dong-A, Eli Lilly, Glenmark, Hope, Hydra, Immune, Novartis, NsGene, Olatec, Phosphagenics, Quark, Reckitt Benckiser, Relmada, Semnur, Syntrix, Teva, Trevena and Vertex. S.N.R. has received a research grant from Medtronic Inc. and honoraria for participation in advisory boards of Allergan, Daiichi Sankyo, Grünenthal USA Inc. and Lexicon Pharmaceuticals. C.E. and T.L. declare no competing interests.

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